

REMARKS

In the Office Action dated May 18, 2006, Claims 1-53, 55, and 59 are pending and rejected.

The above amendment is made to more particularly point out and distinctly claim the subject matter regarded as invention. No new matter is added. Support for the terminology can be found at pages 14-16 and 23 -37 of the specification. The above amendments makes the terminology for compounds or groups having a range of carbon atoms consistent throughout the claims.

New claim 60 is added to claim additional specific subject matter disclosed in the specification.

35 U.S.C. §112, 2nd Paragraph Rejection

Claims 12-33 stand rejected again under 35 U.S.C. § 112, second paragraph as the term "N-C₂-C₆alkanoylC₂-C₆aminoalkyl" is allegedly indefinite. Support for the terminology can be found at pages 14-16 and 23 -37 of the specification where it is clear that "N-C₂-C₆alkanoylC₂-C₆aminoalkyl" is a substituted amine having a first substituent of an alkanoyl group with 2 to 6 carbon atoms and a second substituent of an aminoalkyl group with 2-6 carbon atoms. The above amendment is made to Claims 12-33 have been amended to further clarify this matter and to make the terminology for compounds or groups having a range of carbon atoms consistent throughout the claims.. No new matter is added.

35 U.S.C. §112, 1st Paragraph Rejections

Claims 1-53, 55 and 59 stand rejected under 35 U.S.C. 112 for containing subject matter which was not described in the specification. The Examiner asserts the specification fails to provide a structure activity relationship between the substrate to be cyclized and the thioesterase domain protein.

Applicants strongly disagree. Applicants have discovered that an excised Type 1 thioesterase or thioesterase domain protein can function on its own as an excised fragment to

prepare macrocyclic molecules, thereby obviating traditional synthetic chemistry approaches to macrocyclic molecule synthesis, which generally exhibit low yields, require protecting groups and typically are carried out in organic solvents. Thus, the present invention is directed to and claims

[a] method for the preparation of macrocyclic molecules comprising:
contacting a purified excised thioesterase (TE) domain protein with a substrate for said purified excised thioesterase (TE) domain protein that comprises an activated acyl residue and a pendant nucleophile separated by a linear backbone under conditions conducive to formation of a TE-O-acyl bond such that subsequently the pendant intramolecular nucleophile can displace the TE domain to form the macrocyclic product,

as set forth in claim 1.

The structure activity relationship between the substrate to be cyclized and the thioesterase domain protein is clearly set forth in the specification. What is newly discovered is the fact that the purified excised thioesterase (TE) domain protein can function outside of the biological domain. Once this discovery is known, anyone skilled in the art can practice the invention with any purified excised thioesterase (TE) domain protein.

Applicants submit the Declaration of Professor Christopher T. Walsh, the Hamilton Kuhn Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School, in support of their position. The Walsh Declaration provides support for the fact that there is adequate written description for the claimed invention. The selectivity of the thioesterase domain protein, which is provided by the inclusion of an end group functionality of the natural substrate for the TE domain, is not the invention. As aforesaid, the invention resides in the discovery that the purified excised thioesterase (TE) domain protein can function outside of the biological domain. Examples of such TE domain proteins are clearly described at page 11 of the specification. Additional examples are well known in the art.

The specification provides numerous examples of substrates that are amenable to the cyclization reaction mediated by a TE domain protein. Such substrates, found at least at pages 6-9 of the specification, are described by various generic formulae having common functional

group characteristics. Thus, the substrates for each of the identified TE domains provided by the specification are known such that homologous substrates suitable for macrocyclization by a specified excised TE domain can be readily rationally designed without undue experimentation based on the structural variability provided by the instant specification. However, these are based on the natural substrate for the enzyme. If the natural substrate is not known, the substrate can be determined by routine experimentation.

Applicants therefore contend that the specification provides for a TE domain protein catalyzed cyclization of a substrate, wherein the substrate has a functional group preference for the TE domain protein, which is based on the natural substrate, and that functional group substrate structure is clearly described by the specification. Additionally, Applicants contend that one of ordinary skill in the art would be able to determine a substrate suitable for the claimed TE domain protein mediated cyclization, and that such a determination would be routine experimentation. See Walsh Declaration.

The claimed invention provides a chemical transformation in which a catalyst (the excised TE domain) cyclizes an acyclic substrate having an activated acyl residue and a nucleophile to form a macrocyclic product. The specification provides ample working examples of the claimed chemical transformation and teaches how to identify other catalysts (other TE domains) and substrates which are suitable for use with other catalysts.

Thus, one of skill in the art could predict the structure of a substrate useful in the claimed methods based on the teachings of the specification. Accordingly, claims 1-53, 55, and 59 are fully described and the specification meets the requirement of 35 U.S.C. 112.

Claims 34-53 and 55 stand rejected under 35 U.S.C. 112 for containing subject matter which was not described in the specification. The Examiner asserts that a description for the genus is not adequately described by the specification. It is also asserted that the specification does not provide a teaching on the selection of both the enzyme and substrate and does not provide additional working examples.

The Walsh Declaration shows that there is adequate written description of elongation of organic compounds. Specifically, the Declaration provides that elongation of an organic

substrate involves reaction sequences known to those of ordinary skill in the art, and is a matter of functional group conversions and couplings of at least two reagents. Although the elongation/cyclization process is in competition with hydrolysis as noted by the Examiner, those of ordinary skill in the art are aware of methods to distinguish the two allegedly competing reactions and the different products can be readily separated.

Regarding the working examples, there is no requirement that working examples be given for each and every embodiment of the invention. Applicants have provided one working example, as acknowledged by the Examiner. The specification, at page 45-46 and Fig. 3b-d, provides evidence of at least one elongation-cyclization working example. Thus, the rejection is overcome and withdrawal of the rejection is requested.

This is the type of invention where one working example teaches the generic concept of the invention.

The Trauger, et al. reference (Trauger, *Nature* (2000) 407: 215-218), which is cited on page 11 of the specification, states that PKS systems can produce new polyketides and peptides. See page 216, 1st column of Trauger et al. In addition, as the specification states at the top of page 8, substrate specificity of other excised TE domains can be determined by those skilled in the art by routine procedures. Routine procedures are not considered "undue experimentation" as the Examiner asserts. The Applicants then provide guidance to those skilled in the art as to how to select appropriate TE domains and their substrates. In addition, the specification provides many working examples of the claimed methods. Thus, under the Wands factors, Applicants have fully enabled the scope of the claims because no undue experimentation is necessary, only routine procedures are needed to determine substrates; Applicants provide guidance in the specification as to how to choose TE domains and substrates; many working examples are presented; and those of skill in the art are considered highly skilled.

The rejection is thus overcome and withdrawal of the rejection is requested. If the Examiner intends to maintain these rejections under Section 112, first paragraph, the Examiner is requested to provide evidence or sound scientific arguments why the teachings of the present specification are not adequate to teach and enable the presently claimed invention to one skilled in the art.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' representative would expedite prosecution of this application, the Examiner is cordially invited to call Applicant's undersigned representative.

In view of the above discussion, Applicant believes the pending application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, the Commissioner is hereby authorized and requested to charge Deposit Account No. 04-1105.

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12 April 07

Respectfully submitted,

By

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